sion level of these genes. SVA retrotransposon has a high degree of GC content (~70%) and a large number of CG sites (>150) in its nucleotide sequence, so that it is frequently hypermethylated in its insertion site. In fact, the present study demonstrated that the SVA retrotransposon was hypermethylated in genomic DNA from the caudate nucleus of the patient with XDP (fig. 7), which was also used in northern analysis, quantitative RT-PCR, and in situ hybridization. Such hypermethylated status and high GC content are able to affect dynamics of surrounding nucleotide sequence, such as the *cis*-regulatory element, so SVA insertions may reduce the expression level of adjacent genes. For instance, many large introns of eukaryotes often contain tissue-specific *cis*-regulatory elements, such as enhancers or silencers.[16–22] Intron 32, the largest intron of *TAF1* (29,932 bp), possibly contains a neuron-specific *cis*-regulatory element. Although involvement of other sequence variants in XDP pathogenesis is still possible, it is most likely that the SVA insertion impairs the function of a hypothetical neuron-specific *cis*-regulatory element, such as an enhancer, through changes in the methylation content and then substantially reduces the expressions of many isoforms of TAF1, including TA14-391, in the neurons. Because of the original neuron specificity of the expression, the TA14-391 isoform might represent the impairment more remarkably than do other isoforms. On the other hand, the remaining expression, as shown for TA14-391, despite being low, may compensate for complete loss of function and may account for the relatively late disease onset (age 39.5±8.44 years) and the recessive mode of inheritance.

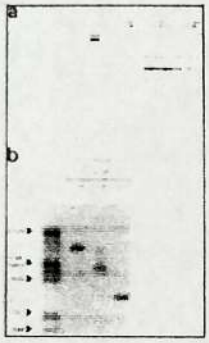

Figure 7.

Detection of methylation around the SVA insertion. *a,* Restriction sites around the SVA insertion. The *Hin*dIII fragment and Southern probe are identical to those in figure 1*a*. The SVA insertion created 47 new *Hpa*II sites in the *Hin*dIII restriction fragment. ...

In summary, our results suggest that the SVA retrotransposon insertion into the *TAF1* gene may cause XDP by altering the expression of TAF1 isoforms, including TA14-391, possibly through DNA methylation changes. To our knowledge, our report is the first to reveal the entire genomic sequence of the *DYT3* region and to demonstrate at least one whole structure of the neuron-specific isoform of TAF1 and the disease-specific mutation, with a possible mechanism. To establish the disease specificity and the involvement mechanism of the SVA insertion in reduced expression of *TAF1* in XDP, further studies, such as an extensive population screening and genetic modification in model organisms, will be necessary and warranted. The TAF1 protein is the largest and the essential component of the TFIID complex in the pathway of RNA polymerase II–mediated gene transcription,[23,24] and it regulates transcription of a large number of genes related to cell division and proliferation.[23–25] How can a ubiquitous gene such as *TAF1* cause a disease that affects a selective part of the nervous system? We hypothesize that the neuron-specific isoforms and/or their enhanced expression level of *TAF1* (table 7) may play important roles in the nondividing cell. Sharing similar pathological features in the caudate nucleus, XDP and Huntington disease might result from disorders in the same biochemical pathway of RNA polymerase II–mediated gene transcription. In Huntington disease, for example, the abnormal huntingtin protein has been shown to interfere with the interaction between Sp1 and TAFII130, resulting in reduced expression of *DRD2* (MIM 126450) in the brain, including the caudate nucleus.[26] In XDP, the decreased expression of the TA14-391 isoform, and probably other TAF1 isoforms, may result in transcriptional dysregulation of many neuronal genes, including *DRD2*. We believe that the present findings in XDP support the concept of "transcription syndromes"[27] in TFIID, which include congenital cataracts facial dysmorphism neuropathy (CCFDN [MIM 604168]) syndrome, caused by a partial deficiency of RNA polymerase II[28]; Huntington disease[26]; dentato-rubro-pallidoluysian atrophy (DRPLA [MIM 125370]),[29] caused by interference in the signals to TFIID; and spinocerebellar ataxia 17 (SCA17 [MIM 607136]),[30] caused by an expanded polyglutamine in the TATA-binding protein (TBP [MIM 600075]).

Acknowledgments

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